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NOTICES

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This technical report has been reviewed and is approved for publication.

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Dose-response curves for atropine- or benactyzine-induced performance decrements were estimated for both humans and monkeys. Monkeys were more tolerant than humans to both drugs, and their dose-response curves were not as steep. Thus, no simple correction coefficient would allow extrapolation of data from one species to the other. However, rough extrapolations could be made for specific levels of performance decrement by using the regression equations or graphs developed from the data analysis.

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BEHAVIORAL EFFECTS OF ATROPINE AND BENACTYZINE: MAN-MONKEY COMPARISONS

INTRODUCTION

The United States Armed Forces have a continuing interest in the pharmacologic treatment of nerve-agent casualties. Nerve agents are cholinesterase inhibitors that cause a constellation of clinical signs relating to nicotinic and muscarinic stimulation. Two antimuscarinic drugs, atropine and benactyzine, have been combined with a cholinesterase reactivator, TMB_4, to provide an emergency field treatment that can be self-administered. This combination has been called TAB, and contains 39.24 mg of TMB_4, 1.03 mg of atropine, and 4.14 mg of benactyzine (approximate ratio of 40:1:4).

Because of the rapid irreversible binding of some nerve agents to cholinesterase, TAB is expected to be most effective if given before or just after exposure to the agent. A complication, however, is that TAB by itself can cause performance decrement and, in the military context, this is a very dangerous side effect. Studies are in progress, therefore, to seek a reformulation of TAB, perhaps by adjusting the ratios by changing the quantity of some of the constituents. A difficulty encountered at this juncture is that data from monkeys and from human beings appear to be very different. The purpose of this report, therefore, is to analyze existing data on human and monkey behavioral responses to atropine and benactyzine to see if a basis of extrapolation from one species to the other can be found.

METHODS

The information for this analysis was derived from published accounts of human responses to benactyzine and to atropine, and from monkey experiments conducted at the USAF School of Aerospace Medicine and the Biomedical Research Laboratory (Aberdeen Proving Grounds, Maryland). Monkeys were *Macaca mulatta* (rhesus) and *Macaca fascicularis* (cynomolgus). Since most studies on human beings reported drug doses in mg per person, and subjects were usually males, the doses were converted to mg/kg by dividing by 75 kg. Oral doses were believed to be somewhat less effective than parenteral doses and were therefore converted to subcutaneous (SQ) or intramuscular (IM) equivalent doses by multiplying by 0.7.

Reported effects from treatment ranged from symptomatic to efficiency of task performance. Tasks were extremely varied, including hole digging, tire changing, number facility tests, and reaction time tests. Because of this diversity, test results were assigned to broad decrement categories by the authors, acting independently. In almost all instances the categorization of tests was the same, and few compromises were necessary to create a useable table for analysis. Categories ranged from 0 to 4: 0 = no effect; .5 = questionable effects; 1 = statistically significant effects on the order of 25% decrement; 2 = approximately a 50% decrement; 3 = approximately a 75% decrement; and 4 = incapacitation. Incapacitation was inferred when task performance

stopped and when individuals were hallucinating or in coma. Results were then cast into dose versus decrement regressions. In most instances, the fit to the regressions was improved when the drug doses were $\log_{10}$ transformed.

RESULTS

Data from human and monkey anticholinergic studies are listed, according to performance decrement category, in Table 1 for atropine and Table 2 for benactyzine. These data were then analyzed by regression, using the decrement category as the dependent variable and the log of drug dose as the independent variable. These equations are reported in Table 3.

From the regression equations in Table 3, one can calculate a drug dose for a given decrement, or the expected decrement from a given dose. However, if one wants to know a drug dose for monkeys (X_m) that represents a known drug dose in humans (X_h), the solution for equivalent levels of performance decrement is to set Y (human) = Y (monkey), X_h is known, and solve for X_m. These solutions are given in Table 4.

DISCUSSION

Perusal of the tables and figures shows that one can estimate many dose-response relationships, for humans and monkeys, and between humans and monkeys. For example, one can address the problem of TAB-induced performance decrement.

By using the regression equations for category .5 (setting Y = .5, a questionable decrement), it can be determined that 0.052 mg/kg atropine and 0.027 mg/kg of benactyzine would be given to a human being. For a 75-kg person, this is 3.90 mg of atropine and 2.03 mg of benactyzine, which is quite different from the 1 mg of atropine and 4 mg of benactyzine in the current TAB. Because benactyzine acts rapidly on the central nervous system (10 to 45 min) and atropine acts slowly (90 min to several hrs), TAB effects can be reasonably predicted by examining each drug separately. Thus, one TAB injection into a person would be expected to cause no detectable effect on performance from the 1 mg of atropine (Fig. 1) and somewhat more than a category 1 decrement (c. 35% decrement) from the 4 mg of benactyzine (Fig. 2). It is unbalanced from the behavioral toxicity viewpoint, and 2.2 mg of atropine could be added to TAB and still not have atropine behavioral toxicity (3.2 mg atropine = category 0).

Another use of the regression equations is in animal modeling. If one were to propose a behaviorally balanced TAB, at category .5 decrement, a reasonable requirement would be to determine the prophylactic or therapeutic effectiveness of this new ratio. Since there is no simple extrapolation of human doses to monkeys (monkeys are far more tolerant, on a mg/kg basis, and their dose-response curves are flatter), the equations in Table 4 allow one to formulate a monkey TAB that has similar behavioral toxicity characteristics of the proposed human TAB. The problem can also be worked the other way; experimentally determine a therapeutically effective atropine or atropine plus benactyzine treatment in monkeys, and then convert this into human behaviorally equivalent doses. However, this only solves the antimuscarinic part of the problem.

TABLE 1. SUBJECTIVE CATEGORIZATION OF ATROPINE-INDUCED PERFORMANCE DECREMENT

Decrement category[a]	Species	Task	Dose[b] (mg/kg)	Ref
0	Human	No. Facility & Mil Fd Tasks	.05	13
0	Monkey	Equilibrium Platform	.044	5
0	Monkey	Timing Task	.044	12
0	Monkey	Equil Plat (M. *mulatta*)	.105	1
0	Monkey	Equil Plat (M. *fascicularis*)	.105	1
.5	Human	Symptoms	.03	11
.5	Human	No. Fac & Mil Fd Tasks	.08	13
.5	Monkey	Equil Plat (M. *mulatta*)	.14	1
.5	Monkey	Equil Plat (M. *fascicularis*)	.14	1
1	Human	Symptoms	.067	2
1	Human	Symptoms	.067	11
1	Human	Behavioral Check List	.089	9
1	Human	Behavioral Check List	.095	9
1	Human	Number Facility	.075	9
1	Monkey	Timing Task	.14	12
2	Human	Behavioral Check List	.13	9
2	Human	Number Facility	.125	9
2	Human	No. Facility & Mil Fd Tasks	.08	13
2	Monkey	Equilibrium Platform	.14	5
2	Monkey	Equil Plat (M. *mulatta*)	.187	11
2	Monkey	Equil Plat (M. *fascicularis*)	.187	1
3	Human	Symptoms	.13	11
3	Human	Behavioral Check List	.135	9
3	Monkey	Timing Task	.44	12
3	Monkey	Equil Plat (M. *mulatta*)	.25	1
3	Monkey	Equil Plat (M. *fascicularis*)	.25	1
4	Human	Symptoms	.13	11
4	Human	Behavioral Check List	.169	9
4	Human	No. Facility	.175	9
4	Monkey	Equilibrium Platform	.44	5

[a] 0 = no effect; .5 = questionable effect; 1 = slight effect (c.25% decrement; 2 = moderate effect (c.50% decrement); 3 = severe effect (c.75% decrement); 4 = incapacitation.

[b] Doses in mg/kg either given by author or derived for humans by dividing by 75 kg.

TABLE 2. SUBJECTIVE CATEGORIZATION OF BENACTYZINE-INDUCED PERFORMANCE DECREMENTS

Decrement category[a]	Species	Task	Dose[b] (mg/kg)	Ref
0	Human	Mental Tests & Time Perception	.053	8
0	Monkey	Equil Platform & Reaction Time	.054	4
0	Monkey	Timing Task	.054	12
.5	Human	Symptoms	.027	10
.5	Human	Symptoms, Piano Playing, & Mental Tasks	.027(.019)	3
.5	Monkey	Equil Platform & Reaction Time	.17	4
1	Human	Mental Tests & Time Percept	.053	8
1	Human	Choice Reaction Time	.07	7
1	Monkey	Timing Task	.17	12
2	Human	Symptoms	.067	10
2	Human	Symptoms, Piano Playing, & Mental Tasks	.093(.065)	3
2	Human	Symptoms, Piano Playing, & Mental Tasks	.12 (.084)	3
2	Human	Symptoms and Military Tasks	.13	14
2	Monkey	Equil Platform & Reaction Time	.54	4
2	Monkey	Timing Task	.54	12
3	Human	Symptoms, Piano Playing, & Mental Tasks	.2 (.14)	3
3	Human	Symptoms & Military Tasks	.13	14
3	Monkey	Equil Platform & Reaction Time	1.70	4
3	Monkey	Timing Task	1.70	4
4	Monkey	Choice Reaction Time, Symptoms	.16	6

[a] 0 = no effect; .5 = questionable effect; 1 = slight effect (c.25% decrement); 2 = moderate effect (c.50% decrement); 3 = severe effect (c.75% decrement); 4 = incapacitation.

[b] Doses in mg/kg either given by author or derived by dividing by 75 kg. Oral dose converted to SQ or IM equivalent by multiplying by 0.7; enclosed in ( ).

TABLE 3. REGRESSION EQUATIONS*

	Human	Monkey
Atropine	$y = 7.571 + 5.515 \log X$	$y = 4.819 + 4.055 \log X$
Std Error (β)	S.E. (β) = 0.980	S.E. (β) = 0.638
Correl Coef	$r = 0.833$	$r = 0.878$
Benactyzine	$y = 5.678 + 3.296 \log X$	$y = 2.502 + 2.052 \log X$
Std Error (β)	S.E. (β) = 0.604	S.E. (β) = 0.118
Correl Coef	$r = 0.876$	$r = 0.990$

* y = performance decrement category; β = slope; x = drug dose in mg/kg.

TABLE 4. EQUIPOTENT EXTRAPOLATION EQUATIONS*

	Human-to-Monkey	Monkey-to-Human
Atropine	$X_m = 4.77\ X_h^{1.36}$	$X_h = .317\ X_m^{.74}$
Benactyzine	$X_m = 35.30\ X_h^{1.61}$	$X_h = .109\ X_m^{.62}$

* X = dose in mg/kg; m = monkey; h = human. Human-to-Monkey means if one has a known level of performance decrement from a known drug dose in humans, this equation will estimate a drug dose to cause a comparable decrement in *Macaca* monkeys, and vice versa for Monkey-to-Human equations. The regression data are also presented graphically in Figure 1 for atropine, and in Figure 2 for benactyzine.

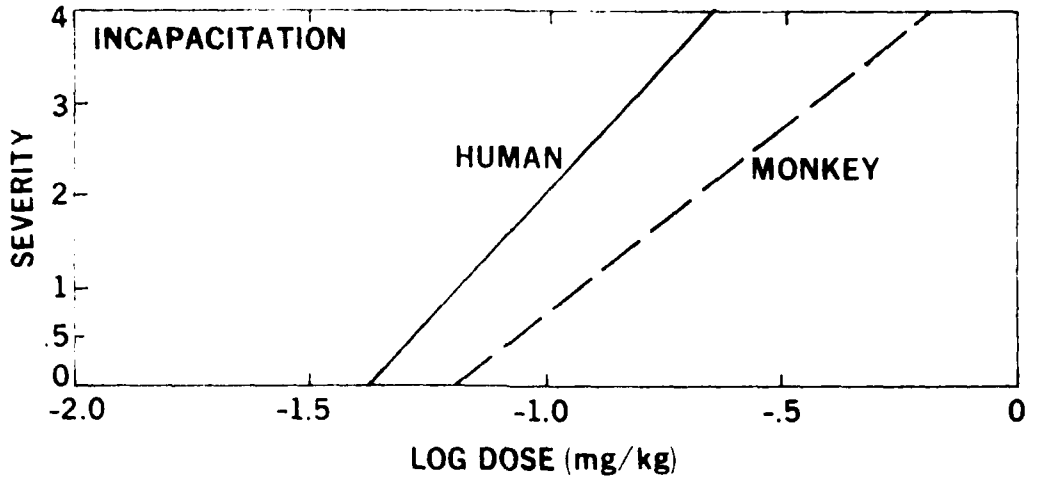

Figure 1. Atropine dose response.

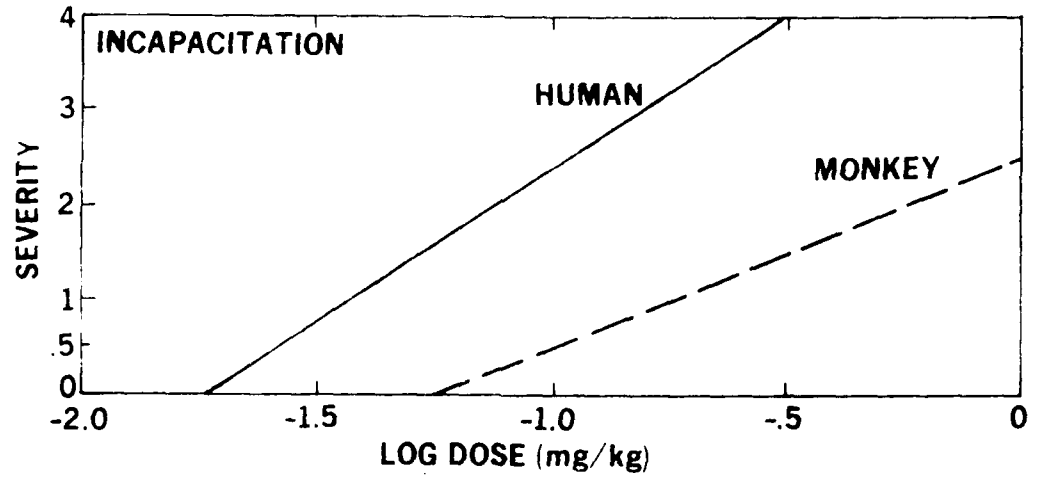

Figure 2. Benactyzine dose response.

The relationship between the sensitivity of the organism to anticholinergics and sensitivity to anticholinesterases is poorly defined. If a consistent relationship were to be found for these stressors, then rather sophisticated modeling of actual nerve-agent effects could be accomplished. At present, the anticholinergic portion of the problem is moderately well understood. More carbamate anticholinesterase dose-response studies, and carbamate-anticholinergic antagonism studies, need to be performed on both humans and animals. If a predictable relationship exists between anticholinergics and carbamates, then one could extrapolate organophosphate data from animals to man with a far greater degree of accuracy and with much more confidence than at present.

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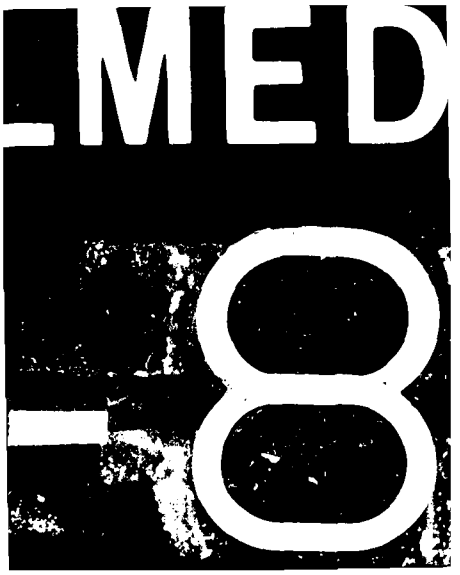
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